**Biotech**: small-to-medium R&D company focused on identification of new molecules for the clinic

**Big Pharma**: medium-to-large companies who develop candidates, perform clinical studies, market, manufacture and commercialize drugs

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**Evolution of a biotech startup**

- **Acquired**: Firm is acquired (66) - 13.3%
- **IPO**: Firm experiences an IPO (51) - 10.2%
- **Going concern**: Firm receives DUNS number ≥ 3, no IPO or acquisition (149) - 29.9%
- **False starters**: Firm receives DUNS number but employees ≤ 2 (90) - 18.1%
- **Non-starter**: Firm never applies for DUNS number (35) - 7.0%
- **Firm fails**: Evidence of failure or no evidence of survival (107) - 21.5%

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**Financing a biotech startup**

- **Non-Dilutive Funding**
  - traditional bank loans or lines of credit
  - non-traditional royalty participation arrangements
- **Angel Investors**
  - development-to-early stage
  - investors have business expertise
  - investors become partial owners
- **Venture Capital**
  - early stage
  - VC firms have biotech expertise
  - higher investment than "angel"

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**Crowdfunding**
- "virtual" method
- large number of investors
- SEC capped it at $1M

**Federal & State Government**
- early stage
- grants/awards to promote biotech research

**Strategic Transactions & Outsourcing**
- startup aligns itself with existing company

**IPO**
- middle-to-late stage
- large amounts of funding

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**Acquisition**: evidence that technology was acquired by other entity

**IPO**: Initial Public Offering (or stock launch)

**Going concern**: evidence of activity and ongoing operations

**Failed firm**: hard evidence (bankruptcy or dissolution) or soft (no website, no press, no current employees)

**False-starter**: evidence of business activity, but lacks human capital

**Non-starter**: technology license, but no evidence of business activity

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**Biotech hubs**

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"The National Law Review 2022, X, 9"
Cetus Corporation
– Founded in Berkeley, CA in 1971
– Founders:
  - Ronald Cape (PhD, MBA)
  - Peter Farley (MD, MBA)
– Prof. Donald Glaser (1960 Nobel Prize in Physics)
  “for the invention of the bubble chamber”
– Notable drug: Recombinant Interleukin-2 (IL-2)
  - Type of cytokine signaling molecule in the immune system that regulates the activities of white blood cells
  - Treatment for kidney cancer
  - Race between Cetus, Genentech, Immunex (now Amgen since 2002) and Prof. Tadatsugu Taniguchi (successful)
  - Cetus created a proprietary recombinant version
  - Approved in 9 European countries, but refused by the FDA

Cetus’s Costly Stumble on IL-2
The failure to win approval for Proleukin sent shock waves through the industry, put Cetus’s stock in a tailspin, and raised doubts about interleukin-2 therapy

Science 1990, 250, 20

– Groundbreaking event: polymerase chain reaction (PCR) technique
  Conceived by Kary Mullis (1993 Nobel Prize in Chemistry)
  “for his invention of the PCR method”
  - Only NP awarded for research done at a biotech company

– Merged with Chiron Corporation (now Novartis since 2006) in 1991 due to IL-2 fiasco
Amgen (Applied Molecular Genetics)
– Founded in Thousand Oaks, CA in 1980
– Notable members of scientific advisory board:
  - Prof. Norman Davidson & Prof. Leroy Hood
  - Both recipients of the National Medal of Science
– Revenue: $26B (2021)
– Total employees: over 24,000 (2022)
– Focus:
  - Molecular biology and biochemistry
  - Techniques based on recombinant DNA (rDNA)

– Notable drugs (produced with rDNA):
  - Epoetin alfa (Epogen) (1989) (WHO List of Essential Medicines)
    Human erythropoietin
    Stimulates erythropoiesis (production of red cells)
    Treatment for anemia
  - Filgrastim (Neupogen) (1991) (WHO List of Essential Medicines)
    Hematopoietic agent
    Stimulates the growth of white cells
    Treatment for cancer patients with bone marrow damage
  - Denosumab (Prolia, Xgeva) (2010)
    Human monoclonal antibody
    Inhibits the maturation of osteoclasts (cells which break down bone tissue)
    Treatment of osteoporosis, treatment-induced bone loss, bone metastases

– Notable drugs (produced through synthetic organic chemistry):
  - Etelcalcetide (Parsabiv) (2016)
    Calcimimetic octapeptide that binds the calcium-sensing receptor (CaSR) in the parathyroid gland
    through a covalent disulfide bond
    Activates receptor to establish the negative feedback loop to raise Ca levels
    Treatment for chronic kidney disease (CKD) patients with secondary hyperparathyroidism (HPT)
Amgen

- Notable drugs (produced through synthetic organic chemistry):
  - **Sotorasib (Lumakras, Lumykras)** (2021)
    First KRAS (Kirsten rat sarcoma virus) oncogene inhibitor which targets the G12C mutation through covalent binding: Sulfa-Michael addition of cysteine residue to acrylamide site
    Treatment for non-small-cell lung cancer (NSCLC) patients
    
    (see Covalent Drugs: Trends, Mechanisms & Warheads, Brendyn Smith, 2022)
  - **Cinacalcet (Sensipar)** (2004)
    Small molecule that acts on the CaSR in the parathyroid gland
    Activates receptor to establish the negative feedback loop to raise Ca levels
    Treatment for parathyroid cancer patients and primary HPT patients with hypercalcemia

**Discovery route:**

**Process route:**

- **Controversy**

**Amgen Agrees to Pay $762 Million for Marketing Anemia Drug for Off-Label Use**

Gilead (early-stage)
- Founded in Foster City, CA in 1987 as Oligogen
- Founder: Michael Riordan (MD)
- Notable member of scientific advisory board through the years:
  - Prof. Jack Szostak (2009 Nobel Prize in Physiology or Medicine) "for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"
- Early support from VC Menlo Ventures
- IPO in 1992 (debut on the NASDAQ raised over $86M)
- Donald Rumsfeld appointed as chairman from 1997-2001
  - Served as Secretary of Defense for Pres. G. Ford and Pres. G.W. Bush
- Revenue: over $27B (2021)
- Total employees: over 13,000 (2022)
- Focus:
  - Antisense therapy (antisense oligonucleotides to target messenger RNA)
  - Antivirals (shifted sole focus to antivirals in 2002 after selling its cancer assets)
  - "evolution from biotech to pharma"
- Notable drugs (produced through synthetic organic chemistry):
  - Tenofovir disoproxil (Viread) (1991) (WHO List of Essential Medicines)
    - Nucleotide analog reverse-transcriptase inhibitor (NtARTI or NtRTI)
    - Selectively inhibits viral reverse transcriptase by incorporating into DNA and causing termination
    - Treatment for HIV-1 infection and chronic Hepatitis B
  - Cidofovir (Vistide) (1996)
    - Nucleotide that selectively inhibits viral DNA polymerases by incorporating into DNA and causing termination
    - Treatment for AIDS patients with cytomegalovirus (CMV) retinitis
  - Oseltamivir (Tamiflu) (1999) (WHO List of Essential Medicines)
    - Prodrug neuraminidase inhibitor with the possibility of alteration of virus particle aggregation and release
      (see Prodrug strategies, Jieyu Gu, 2021)
Biotech: A High Stakes Table for Science

Biogen (Biotechnology Geneva)
- Founded in Geneva, Switzerland in 1978 by a collection of biologists
- Notable founders:
  - Prof. Walter Gilbert (1980 Nobel Prize in Chemistry)
    “for their contributions concerning the determination of base sequences in nucleic acids”
  - Prof. Phillip Sharp (1993 Nobel Prize in Physiology or Medicine)
    “for their discoveries of split genes”
- Merger in 2003 with IDEC Pharmaceuticals
- Revenue: almost $11B (2021)
- Total employees: over 9,000 (2022)
- Focus: neurological diseases

Biogen (Biotechnology Geneva)

BeiGene
- Founded in Beijing, China in 2010
- Founders:
  - Prof. Xiadong Wang
  - John Oyler (MBA, now billionaire)
- Early support from Merck
- IPO in 2016 (debut on the NASDAQ raised over $182M)
- Collaborations with Celgene (2017) and Novartis (2021)
- Amgen acquired 20% in 2019
- Revenue: almost $309M (2021)
- Total employees: over 5,000 (2022)
- Focus: drugs for cancer treatment

Bioverativ
- Notable spin-off:
  - Bioverativ (2016)
    Focus: treatment of hemophilia
  - Efmaroctocog alfa (Eloctate, Elocct)
    • antihemophilic factor synthesized via rDNA
    Sanofi acquired it for over $11B (2018)

Aducanumab (Aduhelm) (2021)
- Amyloid beta (Aβ)-directed monoclonal antibody
- Selectively targets aggregated forms (plaque) of Aβ
- Treatment for Alzheimer’s disease patients
- Originally discovered by Neurimmune (University of Zürich)
- Licensed to and developed by Biogen (2007)

Three F.D.A. Advisers Resign Over Agency’s Approval of Alzheimer’s Drug
The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved this week despite weak evidence that it helps patients.

Notable drugs:
- Tislelizumab
  Programmed cell death protein 1 (PD-1)-directed monoclonal antibody
  Currently in Phases II and III for patients with malignant solid tumors
- Zanubrutinib (Brukinsa) (2019)
  Burton’s tyrosine kinase (BTK) inhibitor which targets an active site through covalent binding: Sulfa-Michael addition of cysteine residue to acrylamide site
  Treatment for various lymphomas
  (see Kinase Inhibitors: An Introduction, David Peters, 2019)